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Effect of Brønsted acids on the thiophenol-mediated radical addition–translocation–cyclization process for the preparation of pyrrolidine derivatives

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ABSTRACT

A thiophenol-mediated method for the conversion of propargylamines to pyrrolidines under acidic conditions is described. This cascade reaction involves addition of a thiyl radical to the terminal alkyne followed by a 1,5-hydrogen transfer (radical translocation) and a rapid cyclization affording the pyrrolidine ring. Our studies reveal that complete protonation of the tertiary amine with 10 equivalents of trifluoroacetic acid avoids undesired hydrogen atom abstractions by the thiyl radicals.

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Radical reactions are now part of the arsenal of reactions that synthetic organic chemists use for the preparation of complex molecules [1,2]. Their mildness and functional group tolerance make them particularly attractive for the synthesis of highly functionalized compounds and their reactivity has permitted some unusual transformations. Among all radical reactions, the activation of aliphatic C–H bonds via hydrogen atom transfer (HAT) is a truly unique synthetic tool [3–7]. The preparation of five-membered ring via radical translocation–cyclization (RTC) processes involving transient alkenyl radicals proved to be a particularly efficient process [8]. Alkenyl radicals can be generated directly from alkenyl halides [9,10] or by radical addition to a terminal alkyne [11–19]. The thiophenol-mediated radical addition–translocation–cyclization (RATC) process [20–23] is preparatively very useful since terminal alkynes are easily accessible [24]. It has been used to prepared simple and fused cyclopentanes as well as spirocyclic compounds such as (–)-erythrodiene [22,23,25]. Starting from homopropargylic amines and amides, it was also possible to prepare the heterocyclic systems related to the indolizidine and pyrrolizidine alkaloid skeleton (Scheme 1) [26].

However, all attempts to extend the thiophenol-mediated RATC reaction to the easily prepared propargylic amines failed and a complex mixture of products was obtained (Scheme 2). This result was interpreted as a consequence of undesired hydrogen atom abstraction from the propargylic position leading to stabilized 1-aminosubstitued propargylic radicals. This degradation pathway is well established since Bertrand et al. have described the isomerization of allylic amines under closely related reaction conditions [27,28].

Interestingly, Bietti et al. have recently demonstrated that the rate of hydrogen atom abstraction from the α-position of tertiary alkylamines by the cumyloxyl radical can be lowered by protonation of the amine (Scheme 3) [5,29]. The authors showed that the rate constant for hydrogen atom abstraction from the α-C–H bonds decreased drastically upon protonation of the nitrogen. This observation was rationalized by a decrease in hyperconjugative overlap between the α-C–H σ^* orbital and the nitrogen lone-pair. Therefore, we decided to examine the effect of acid additives on the thiophenol mediated RATC process involving propargylic amines.

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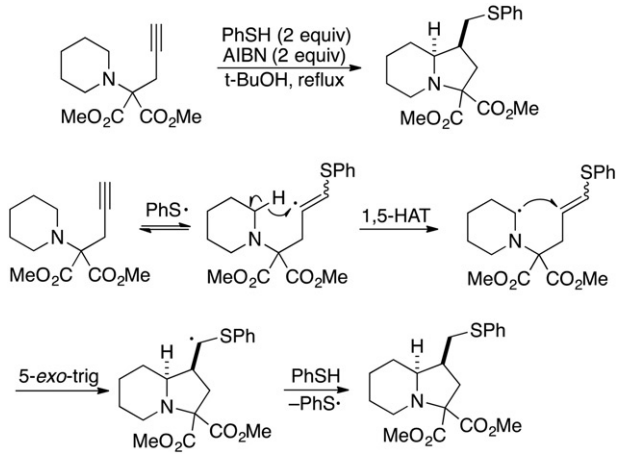
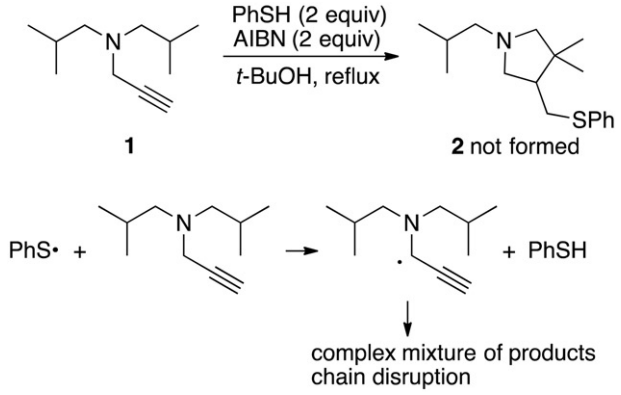
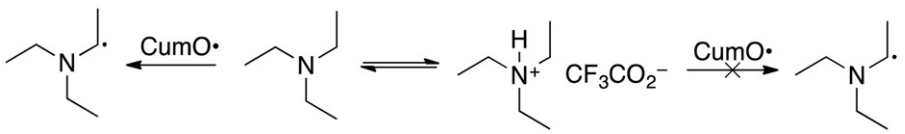
N,N-diisobutylpropargylamine (**1**) was chosen as a model substrate for the preliminary study. This compound was easily prepared by the alkylation of diisobutylamine with propargyl bromide in the presence of potassium carbonate. In order to be compatible with the presence of acid additives, acetonitrile was used as a solvent instead of *tert*-butanol employed for the thiophenol-mediated RATC processes [23]. For the optimization process, reaction yields were determined by gas chromatography and the results are summarized in Table 1. Without additive, the starting material was fully consumed and a complex mixture of products was obtained, with the expected cyclopentane product **2** obtained in only 4% yield. Adding four equivalents of acetic acid did not improve the reaction (Table 1, entry 2).



Scheme 1



Scheme 2

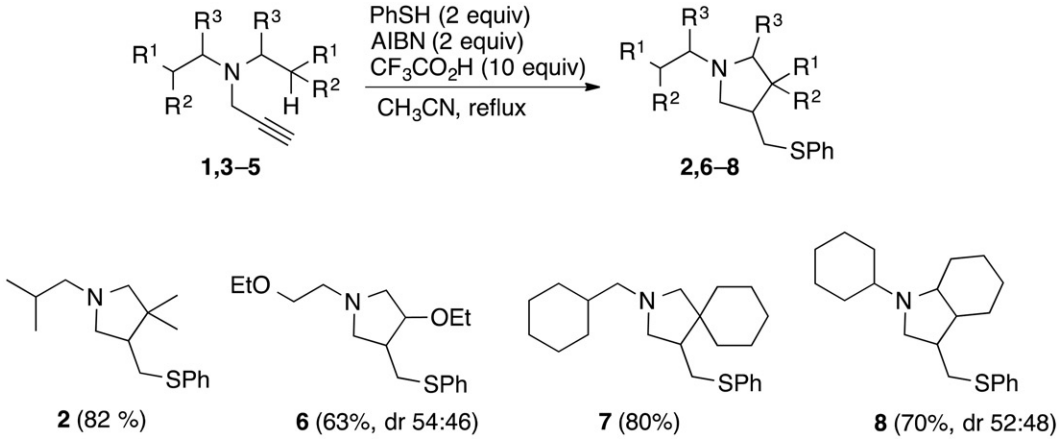


Scheme 3

This is not fully surprising since in acetonitrile, acetic acid (pKa (CH_3CN) = 22.3) is less acidic than the trialkylammonium ion (pKa (CH_3CN) 18.5) [30]. However, running the reaction in pure acetic acid as a solvent led to an increased yield of 25% for **2** (Table 1, entry 3). Stronger Brønsted acids were tested next. Trifluoroacetic acid (pKa (CH_3CN) 12.7) [30] influenced positively the reaction when 1.1 equivalents were used (Table 1, entry 4, 18% yield). The yield increased further when five equivalents were used (Table 1, entry 5, 54% yield) and the best yield was achieved with 10 equivalents (Table 1, entry 6, 78% yield). Larger excesses (Table 1, entries 7 and 8) did not increase further the yield of the reaction. The use of trifluoromethanesulfonic acid (CF_3SO_3H, pKa (CH_3CN) 0.7) [30] was examined next. A low yield of 16% was obtained with 0.9 equivalent (Table 1, entry 9). With 1.0 and 1.5 equivalents, the reaction proceeded more efficiently (Table 1, entries 10 and 11, 68% and 70% yield, respectively). Larger excess of trifluoromethanesulfonic acid did not help. Indeed, in the presence of 10 equivalent of trifluoromethanesulfonic acid, the product was formed in 49% yield (Table 1, entry 12). Based on all these experiments, the use of trifluoroacetic acid (10 equivalents) was selected to run the final solvent optimization. Acetic acid and 1,2-dichloroethane were tried first and gave low yields (Table 1, entries 13 and 14). Benzene (Table 1, entry 15) gave a better result (65% yield) but still inferior to the one obtained in acetonitrile (Table 1, entry 6).

Table 1. Thiophenol promoted RATC reaction with model substrate **1**.

Entry	solvent	acid	equivalents	Yield (GC)
1	CH_3CN	–	–	4%
2	CH_3CN	CH_3CO_2H	4	4%
3	CH_3CO_2H	–	solvent	25%
4	CH_3CN	CF_3CO_2H	1.1	18%
5	CH_3CN	CF_3CO_2H	5	54%
6	CH_3CN	CF_3CO_2H	10	78%
7	CH_3CN	CF_3CO_2H	20	74%
8	CH_3CN	CF_3CO_2H	50	73%
9	CH_3CN	CF_3SO_3H	0.9	16%
10	CH_3CN	CF_3SO_3H	1	68%
11	CH_3CN	CF_3SO_3H	1.5	70%
12	CH_3CN	CF_3SO_3H	10	49%
13	CH_3CO_2H	CF_3CO_2H	10	25%
14	$ClCH_2CH_2Cl$	CF_3CO_2H	10	14%
15	benzene	CF_3CO_2H	10	65%



Scheme 4

The fact that good yields were obtained either with a large excess of CF_3CO_2H (10 equivalents) or with at least one equivalent of CF_3SO_3H indicates that full protonation of the amine is necessary for an efficient reaction. As demonstrated by the reaction run with only 0.9 equivalent of CF_3SO_3H (Table 1, entry 9), a small amount of the free amine (10 mol% in this case) is sufficient to cause a massive decrease in the yield.

The best reaction conditions identified for substrate **1** based on GC yields (Table 1, entry 6), that is, the use of an excess of thiophenol (2 equivalents), AIBN (2 equivalents) and trifluoroacetic acid (10 equivalents) in refluxing acetonitrile as solvent, were used for preparative reactions using the four substrates **1**, **3**–**5** (Scheme 4). In all four cases, the desired cyclized products were isolated in good yields despite the fact the cyclic amines **2**, **6**–**8** are difficult to purify by flash chromatography due to their basic character.

In conclusion, the results presented here demonstrate that the concept of acid-mediated inhibition of undesired hydrogen atom transfers between cumyloxyl radicals and tertiary amines developed by Bietti and Salamone can be extended to thiyl radicals and it represents a key strategy to control reactions of tertiary amines prone to facile hydrogen atom abstraction. When a complex reaction cascade such as the RATC process is involved, full protonation of the amino group by a 10-fold excess of trifluoroacetic acid is required to overcome the strong hydrogen atom donor ability of propargylic tertiary amines.

Disclosure statement

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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